Ortho-McNeil Pharmaceutical, Inc.
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IMPORTANT
DRUG WARNING

Dear Healthcare Professional:

The prescribing information for TOPAMAX® (topiramate/topiramate capsules) Tablets/Sprinkle Capsules has been revised to include a warning that TOPAMAX causes hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate). TOPAMAX is approved and marketed for the adjunctive treatment of partial-onset seizures, generalized tonic-clonic seizures and seizures associated with the Lennox-Gastaut syndrome in adults and children two years of age and older.

Data on hyperchloremic, non-anion gap metabolic acidosis are derived from placebo-controlled trials and post-marketing experience in over 2.5 million patients. In clinical trials, the rate of occurrence of a persistently decreased serum bicarbonate ranges from 23-67% for patients treated with topiramate and 1-10% for placebo. The incidence of markedly low serum bicarbonate in clinical trials ranges from 3-11% for topiramate and 0 to <1% for placebo.

Generally, decreases in serum bicarbonate occur soon after initiation of topiramate, although they can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate, with an average decrease of 4 mEq/L at daily doses of 400 mg in adults and approximately 6 mg/kg/day in pediatric patients. Rarely, patients can experience decrements to values below 10 mEq/L.

Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the

risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

The following has been added to TOPAMAX prescribing information:

Under WARNINGS

Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut Syndrome or refractory partial onset seizures was 67% for TOPAMAX

(at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

Although not approved for the prophylaxis of migraine, the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

Under PRECAUTIONS:

Laboratory Tests

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see WARNINGS).

Pediatric Use:

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia (rickets) and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see WARNINGS).

Under OVERDOSAGE:
Topiramate overdose has resulted in severe metabolic acidosis (see WARNINGS).

You can further our understanding of adverse events by reporting all cases to Ortho-McNeil at the contact numbers listed below or to the FDA MedWatch Program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), by mail (using postage-paid form to MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787) or via www.accessdata.fda.gov/scripts//medwatch/.

A copy of the full Prescribing Information is enclosed for your reference. If you have any questions regarding TOPAMAX tablets and TOPAMAX Sprinkle Capsules, please feel free to call Ortho-McNeil Medical Affairs Division at 1-800-682-6532.

Sincerely,

Joseph Hulihan, MD
Group Director, CNS Research